Effect of Continuous Epinephrine Infusion on Survival in Critically Ill Patients. A Meta-Analysis of Randomized Trials

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Abstract: OBJECTIVES Epinephrine is frequently used as an inotropic and vasopressor agent in critically ill patients requiring hemodynamic support. Data from observational trials suggested that epinephrine use is associated with a worse outcome as compared with other adrenergic and nonadrenergic vasoactive drugs. We performed a systematic review and meta-analysis of randomized controlled trials to investigate the effect of epinephrine administration on outcome of critically ill patients. DATA SOURCES PubMed, EMBASE, and Cochrane central register were searched by two independent investigators up to March 2019. STUDY SELECTION Inclusion criteria were: administration of epinephrine as IV continuous infusion, patients admitted to an ICU or undergoing major surgery, and randomized controlled trials. Studies on epinephrine administration as bolus (e.g., during cardiopulmonary resuscitation), were excluded. The primary outcome was mortality at the longest follow-up available. DATA EXTRACTION Two independent investigators examined and extracted data from eligible trials. DATA SYNTHESIS A total of 5,249 studies were assessed, with a total of 12 studies (1,227 patients) finally included in the meta-analysis. The majority of the trials were performed in the setting of septic shock, and the most frequent comparator was a combination of norepinephrine plus dobutamine. We found no difference in all-cause mortality at the longest follow-up available (197/579 [34.0%] in the epinephrine group vs 219/648 [33.8%] in the control group; risk ratio = 0.95; 95% CI, 0.82-1.10; p = 0.49; I = 0%). No differences in the need for renal replacement therapy, occurrence rate of myocardial ischemia, occurrence rate of arrhythmias, and length of ICU stay were observed. CONCLUSIONS Current randomized evidence showed that continuous IV administration of epinephrine as inotropic/vasopressor agent is not associated with a worse outcome in critically ill patients.

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Alessandro Belletti, MD[1]; Adam Nagy, MD[1,2]; Marianna Sartorelli, MD[1]; Marta Mucchetti, MD[1]; Alessandro Putzu, MD[3]; Chiara Sartini, MD[1]; Federica Morselli, MD[1]; Pierfrancesco De Domenico, MD[1]; Alberto Zangrillo, MD[1,4]; Giovanni Landoni, MD[1,4]; Rosalba Lembo, MSc[1]

Objectives: Epinephrine is frequently used as an inotropic and vasopressor agent in critically ill patients requiring hemodynamic support. Data from observational trials suggested that epinephrine use is associated with a worse outcome as compared with other adrenergic and nonadrenergic vasoactive drugs. We performed a systematic review and meta-analysis of randomized controlled trials to investigate the effect of epinephrine administration on outcome of critically ill patients.

Data Sources: PubMed, EMBASE, and Cochrane central register were searched by two independent investigators up to March 2019.

Study Selection: Inclusion criteria were: administration of epinephrine as IV continuous infusion, patients admitted to an ICU or undergoing major surgery, and randomized controlled trials. Studies on epinephrine administration as bolus (e.g., during cardiopulmonary resuscitation), were excluded. The primary outcome was mortality at the longest follow-up available.

Data Extraction: Two independent investigators examined and extracted data from eligible trials.

Data Synthesis: A total of 5,249 studies were assessed, with a total of 12 studies (1,227 patients) finally included in the meta-analysis. The majority of the trials were performed in the setting of septic shock, and the most frequent comparator was a combination of norepinephrine plus dobutamine. We found no difference in all-cause mortality at the longest follow-up available (197/579 [34.0%] in the epinephrine group vs 219/648 [33.8%] in the control group; risk ratio = 0.95; 95% CI, 0.82–1.10; $p = 0.49$; $I^2 = 0\%$). No differences in the need for renal replacement therapy, occurrence rate of myocardial ischemia, occurrence rate of arrhythmias, and length of ICU stay were observed.

Conclusions: Current randomized evidence showed that continuous IV administration of epinephrine as inotropic/vasopressor agent is not associated with a worse outcome in critically ill patients. (*Crit Care Med* 2019; XX:00–00)

Key Words: catecholamines; hemodynamic management; inotropes; intensive care unit; shock; vasopressors

[1]Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy.

[2]Károly Rácz School of PhD Studies, Semmelweis University, Budapest, Hungary.

[3]Department of Anesthesiology, Pharmacology, Intensive Care, and Emergency Medicine, Geneva University Hospital, Geneva, Switzerland.

[4]Vita-Salute San Raffaele University, Milan, Italy.

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For information regarding this article, E-mail: mucchetti.marta@hsr.it

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Administration of inotropes and vasopressors is frequently required in critically ill patients to restore and maintain adequate tissue perfusion (1). Among the different drugs available, catecholamines remain the most commonly used. However, the choice of the optimal molecule in the different clinical settings remain controversial, and available data are insufficient to provide clear recommendations (2–8).

Epinephrine (or adrenaline) is a catecholamine with high affinity for both alpha and beta-adrenergic receptors (9). Epinephrine is a frequently used vasopressor and inotropic agent in a wide range of clinical settings, especially in patients with severe cardiogenic shock or postcardiac surgery myocardial stunning (10). However, several studies suggest that administration of epinephrine is associated with several side effects, including increase in lactate levels (11), and even a worse outcome in cardiogenic shock patients (12, 13). Nevertheless, a

clear detrimental effect on survival was never demonstrated in randomized controlled trials (RCTs) (11, 14).

The aim of the present systematic review and meta-analysis was to investigate the effect on survival of continuous epinephrine infusion versus any control treatment in critically ill patients.

MATERIALS AND METHODS

The present systematic review and meta-analysis of RCTs was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and following Cochrane Collaboration recommendations (15–18).

Search Strategy and Study Selection

RCTs comparing continuous epinephrine infusion versus treatment with any different kind of vasopressor and inotropic agents were included in this study. No exclusion by language or publication date was enforced. The PICOS criteria were followed: Population (patients admitted to an ICU or undergoing major surgery); Interventions (administration of continuous IV epinephrine infusion); Comparison intervention (other inotropes/vasopressors, placebo, or standard treatment); Outcome (survival); and Study design (RCTs).

In details, inclusion criteria were: administration of epinephrine as IV continuous infusion, critically ill patients (defined as patients admitted to an ICU or undergoing major surgery), and RCTs. Exclusion criteria were: epinephrine administration as boluses (e.g., during cardiopulmonary resuscitation), non-IV administration of epinephrine, neonatal studies, nonhuman studies, lack of data for outcome of interest, studies published as abstract only, and overlapping population.

We searched PubMed, EMBASE, and Cochrane central register of controlled trials databases from inception up to March 31, 2019. Backward snowballing was applied to retrieve additional manuscripts. Eligibility assessment was performed independently by two investigators at title/abstract level and the final selection of included articles was based on complete manuscripts with disagreements solved by consensus.

Data Extraction

Two authors independently collected details on baseline characteristics, periprocedural, and outcome data. These were verified by a third author. We extracted data following the intention-to-treat principle whenever possible. To gather additional data, we contacted corresponding authors via e-mail.

Outcomes

The primary outcome was mortality at the longest follow-up available. Secondary outcomes were 28-/30-day mortality, myocardial ischemia, need for renal replacement therapy, new-onset arrhythmias (any type), supraventricular arrhythmias, ventricular arrhythmias, stroke, bowel ischemia, limb ischemia, length of ICU stay, serum lactate levels 24 hours after randomization (or at the available time-point closest to 24 hr after randomization), and heart rate 24 hours after randomization (or at the available time-point closest to 24 hr after randomization). Outcomes were defined according to individual studies Author's definition.

Statistical Analysis

We calculated individual and pooled risk ratio (RR) for dichotomous outcomes with 95% CIs. For continuous variables, mean difference (MD) with corresponding 95% CI were calculated. Continuous variables reported as median and interquartile range or range were converted into mean and SD (19).

Heterogeneity analysis was performed with Cochran Q statistic and quantified with I^2. Heterogeneity with an I^2 greater than 25% was considered significant: fixed-effect and random-effects models were used in case of low and high statistical heterogeneity.

Publication bias small study effect for primary endpoint was assessed with visual assessment of funnel plot (20). For pooled outcome analyses, a p value of less than or equal to 0.05 was considered significant.

Risk of bias was assessed following the recommended seven items-tool of Cochrane Collaboration (randomized sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, other bias) (21). Each item was evaluated by two trained investigators and an overall judgment of low, high, or unclear risk of bias provided. Studies were classified as "high risk of bias" if they had at least one item reported as high risk of bias, at "unclear risk of bias" if they had at least one item judged to carry an unclear risk of bias, and at low risk of bias if all of the item were at low risk of bias.

In addition to the primary analysis including all included trials, we performed the following subgroup analyses: adult versus pediatric trials, septic versus nonseptic patients, and different control treatment.

The following sensitivity analyses were performed as follows: low risk of bias trials only; sequential removal of each individual trial; change of analysis methods; and change of summary statistics.

We used RevMan 5.3. software (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

A total of 5,249 references were examined at a title/abstract level. After initial screening, a total of 45 studies were retrieved as complete articles. After exclusion of further 33 trials that did not met inclusion criteria, a total of 12 studies randomizing 1,227 patients were included in the analysis (**Fig. 1**) (10, 11, 14, 22–30). Details of major exclusions and reason for exclusion are provided in the **Supplementary Appendix** (Supplemental Digital Content 1, http://links.lww.com/CCM/F177).

Trials' Characteristics

Characteristics of included trials are reported in **eTables 1** and **2** (Supplemental Digital Content 1, http://links.lww.com/CCM/F177). The majority of trials were performed in septic shock (seven trials, 644 patients) (11, 23–25, 27–29) followed

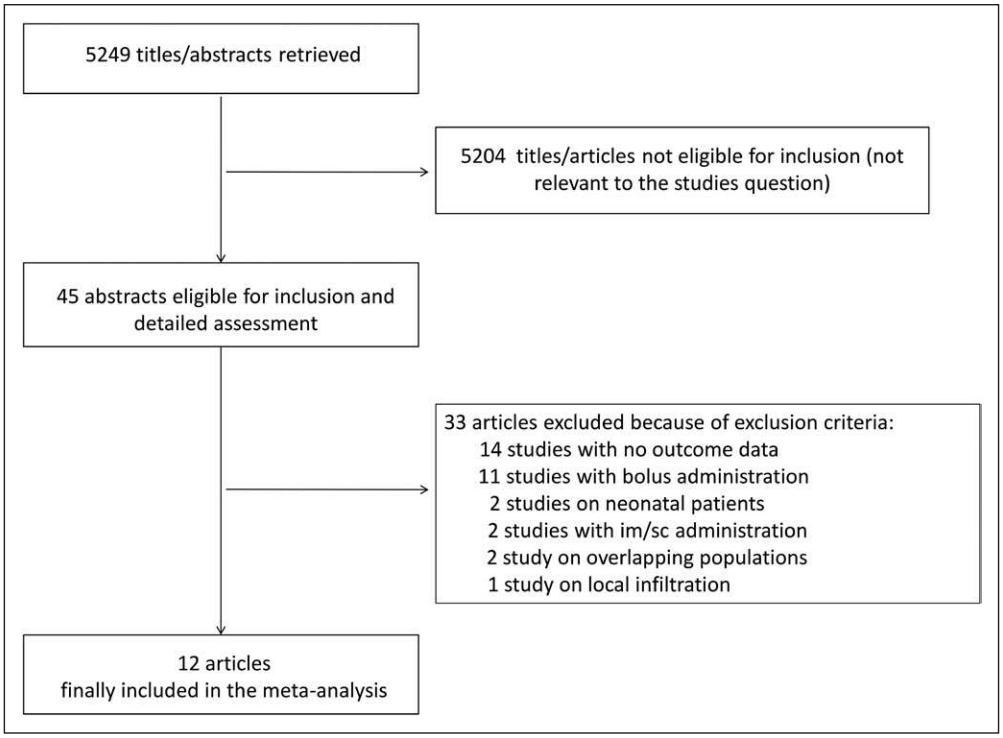

Figure 1. Flowchart for included trials. im = intramuscular, sc = subcutaneous.

by cardiogenic shock (two trials, 87 patients) (10, 22), cardiac surgery (26), mixed ICU patients (14), and major noncardiac surgery (30) (one trial each) settings. Two trials were performed in the pediatric setting (180 patients) (25, 29).

The most frequent control treatment was a combination of dobutamine plus norepinephrine (four trials, 412 patients) (11, 22, 23, 27), with one trials using placebo as control (30) and one trial using levosimendan (26). All other RCTs compared epinephrine against another catecholamines.

Overall, risk of bias analysis showed that two included trials were at low risk of bias (11, 25) (accounting for 390 patients [31.8% of overall included patients]). A total of four trials were considered at high risk of bias (10, 22, 26, 28) (190 patients [15.5%]), and six at unclear risk of bias (**Fig. 2**) (14, 23, 24, 27, 29, 30) (647 patients [52.7%]).

All-Cause Mortality

Overall, we found no difference in all-cause longest follow-up mortality (197/579 [34.0%] in the epinephrine group vs 219/648 [33.8%] in the control group; RR = 0.95; 95% CI, 0.82–1.10; p for effect = 0.49; I^2 = 0%) (**Fig. 3**).

Sequential removal of each trial did not change magnitude and direction of treatment effect (lowest RR = 0.89; 95% CI, 0.73–1.09; p = 0.27; I^2 = 0%; removing Annane et al (11) and highest RR = 0.99; 95% CI, 0.85–1.14; p = 0.87; I^2 = 0%; removing Ventura et al [29]). Selecting only low risk of bias trials did not change magnitude and direction of the results (98/190 [51.6%] in the epinephrine group vs 103/200 [51.6%] in the control group; RR = 1.00; 95% CI, 0.83–1.21; p = 0.99; I^2 = 0%, with two trials included). Changes of the summary statistics from RR to odds ratio or risk difference did not result in a change in significance of study findings. Similarly, for analysis with low heterogeneity, changing from fixed- to random-effects model did not alter significance of the results.

Visual inspection of funnel plot did not suggest presence of significant publication bias (**eFig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F177).

Secondary Outcomes

We found no statistically significant differences in the occurrence rate of any of the secondary outcomes (**Table 1**; and **eFigs. 2–13**, Supplemental Digital Content 1, http://links.lww.com/CCM/F177)

Subgroup Analyses

When studying adult versus pediatric studies (**eTables 3** and **4** and **eFigs. 14–39**, Supplemental Digital Content 1, http://links.lww.com/CCM/F177) we found significant subgroup interaction on serum lactate levels, with lower lactate level in pediatric patients receiving epinephrine as compared with control group (MD for pediatric trials = –0.63 mmol/L; 95% CI, –1.11 to 0.14; p = 0.01; I^2 = 0%; p for interaction = 0.02) (eTable 3 and eFig. 19, Supplemental Digital Content 1, http://links.lww.com/CCM/F177).

We also found a significant interaction between septic and nonseptic trials in serum lactate levels (p for interaction < 0.001), with high serum lactate levels in the epinephrine group in nonseptic trials (eTable 4 and eFigure 31, Supplemental Digital Content 1, http://links.lww.com/CCM/F177).

DISCUSSION

We performed a systematic review ad meta-analysis of RCTs to investigate the effect of epinephrine administration on major clinical outcome of critically ill patients. We found that IV continuous administration of epinephrine as inotrope/vasopressor in critically ill patients did not result in increased mortality or differences in clinically relevant or safety outcomes. However, our systematic literature search highlighted that, despite the widespread use of epinephrine, only 12 RCTs overall randomizing a total of 1,227 patients reported mortality data. Therefore, our results should be considered hypothesis-generating and underline the need for higher quality RCTs on epinephrine use.

We found a possible subgroup interaction effect in serum lactate levels between trials performed in the setting of sepsis and other settings, with higher lactate level in the nonseptic group. However, data from nonseptic trials derived from

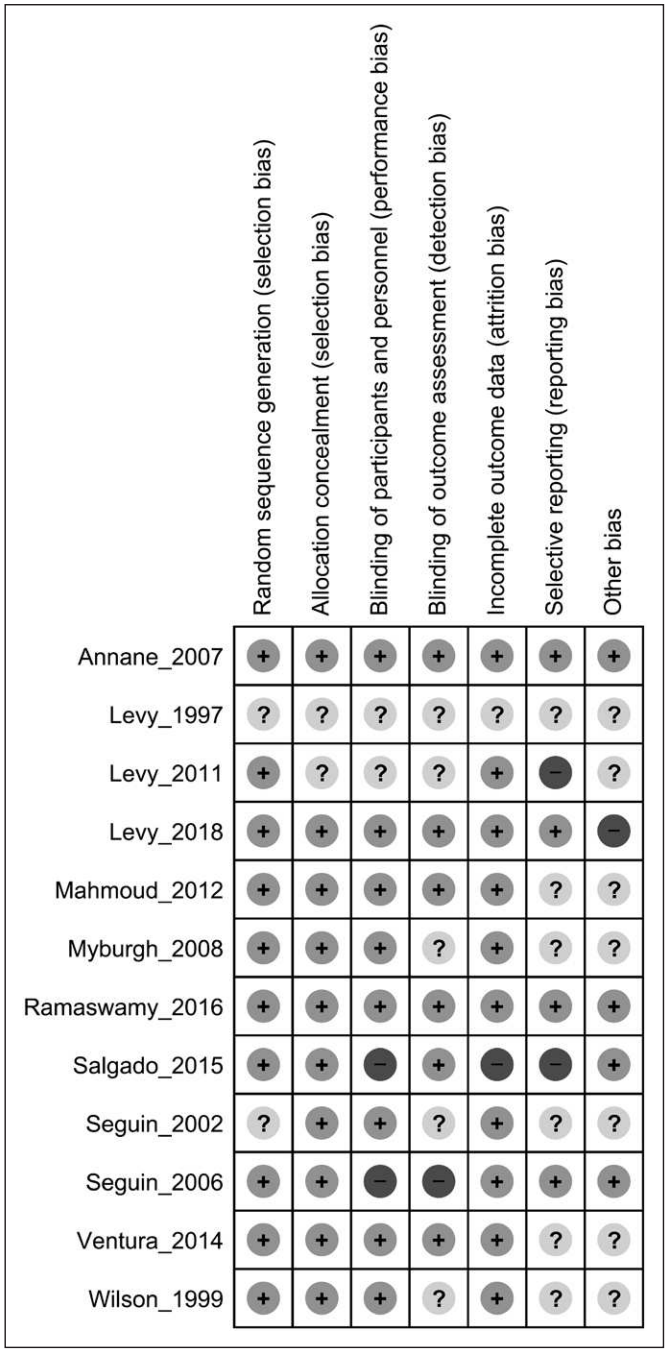

Figure 2. Risk of bias summary.

one small, single trial in patients with cardiogenic shock. Therefore, we believe these results should be interpreted with caution. Furthermore, we observed lower lactate level in pediatric patients receiving epinephrine as compared with control group.

This is the first meta-analysis of RCTs investigating the role of epinephrine in critically ill patients outside the specific setting of cardiopulmonary resuscitation. Our systematic literature search identified several trials comparing epinephrine with other vasopressors in critically ill patients. The largest trial performed so far compared epinephrine versus a combination of norepinephrine and dobutamine in 330 patients with septic shock (11). In this multicenter RCT, no major differences between the two groups were found, with the exception of a higher lactate levels in the epinephrine group which tended to disappear after 4 days. Another multicenter RCT by Myburgh et al (14) compared the effect of epinephrine and norepinephrine in 280 mixed ICU patients and confirmed no difference in mortality between epinephrine and norepinephrine and an higher occurrence rate of lactic acidosis in the epinephrine group. In contrast to these findings, a recent observational trial suggested that epinephrine use might be associated with higher mortality rates in patients with cardiogenic shock (12). This latter study was limited by the observational design, which does not allow to fully adjust for potential biases in treatment selection and baseline characteristics, as underlined by the AltShock group (31). In particular, the AltShock group underline that epinephrine is generally administered to the patients showing the most severe degree of hemodynamic compromise, frequently as a second-line agent. Therefore, it is not surprising that patients receiving epinephrine generally have a worse outcome than patients receiving other vasoactive agents such as norepinephrine or dobutamine (32).

Léopold et al (13) recently published a meta-analysis on the use of epinephrine in the specific setting of cardiogenic shock and found increased mortality associated with epinephrine use. Compared with the present work, the meta-analysis by Léopold et al (13) mainly included data from observational trials, with only one RCT specifically comparing epinephrine with another vasopressor included (10). Accordingly, we believe that findings from Léopold et al (13) provide interesting clues but are limited by intrinsic biases of observational trials. Finally, a Cochrane review investigating different vasoactive strategies for the treatment of cardiogenic shock/low cardiac output syndrome was able to identify only one RCT assessing epinephrine use, with a very low quality of evidence and no difference in mortality between epinephrine and control treatment (33).

Our results suggest that, despite concerns raised by observational trials, use of low-dose epinephrine as an inotrope/vasopressor in critically ill patients does not result in a worse outcome. Epinephrine is a potent catecholamine with a strong affinity for both β- and α-adrenergic receptors and provides positive inotropism, chronotropism, and vasoconstriction (9). Therefore, it is generally used when both an increase in cardiac output and mean arterial pressure are required, the most typical setting being myocardial stunning following cardiac surgery and cardiogenic shock, while it is generally considered a second-line agent in septic shock. Results of our study confirm the general finding that the choice of the inotrope does not seem to have a major impact on clinical outcomes, providing that adequate hemodynamic parameters, oxygen delivery, and tissue perfusion are maintained. Accordingly, the use of epinephrine in ICU should not be discouraged, if both positive inotropism and vasoconstriction are required and the treating physician is more familiar with epinephrine than with other vasoactive agents or when a single agent if preferred. Current guidelines on management of cardiogenic and septic

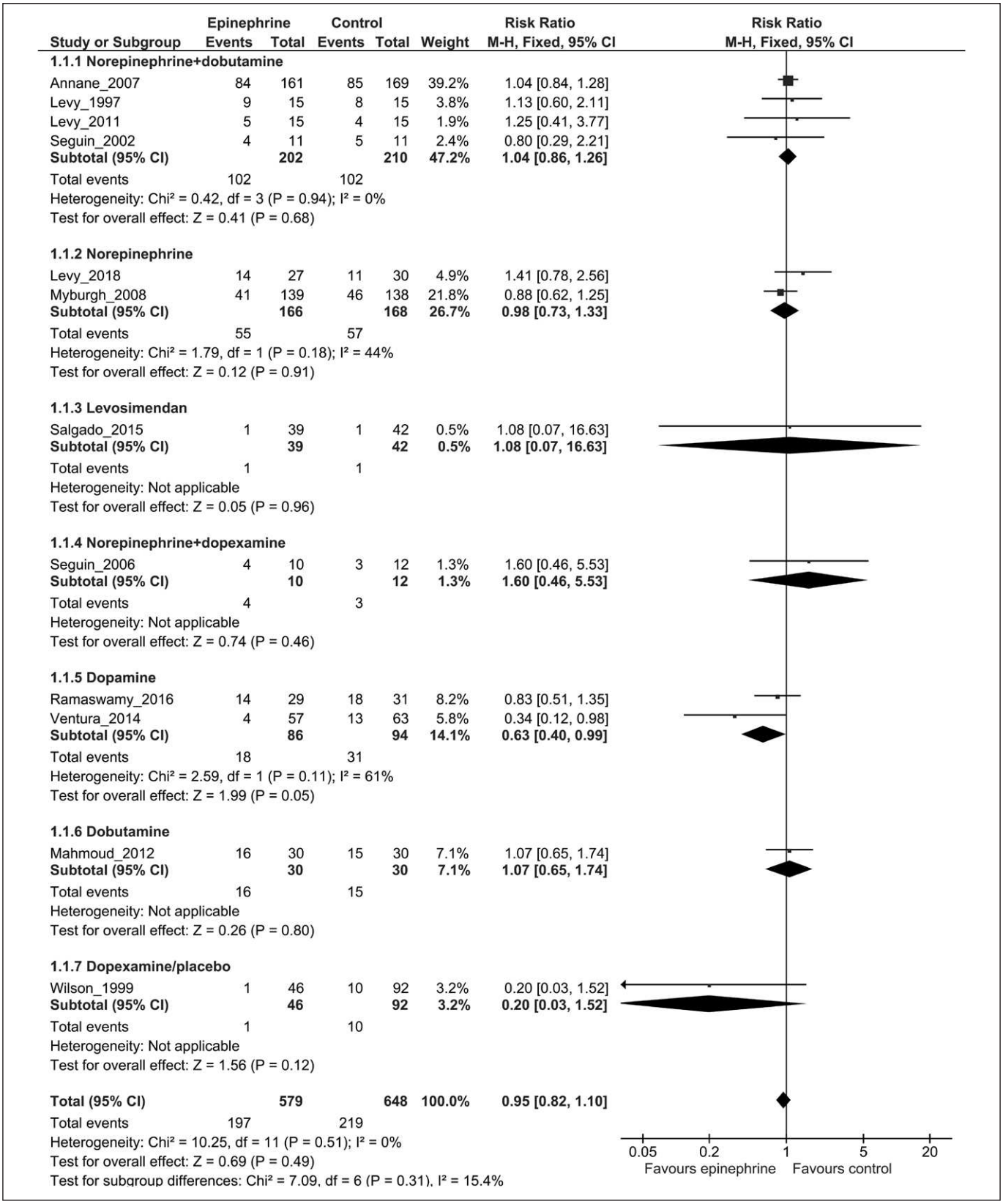

Figure 3. Forest plot for all-cause mortality. *df* = degrees of freedom, M-H = Mantel-Haenszel.

shock recommend norepinephrine as first-line vasopressor, with epinephrine as rescue drug (2, 4, 6, 7). Our results should reassure intensivists and anesthesiologists that epinephrine is a safe alternative to norepinephrine. This might be particularly important in low-resource settings, as the costs of epinephrine are generally lower than other catecholamines. For

TABLE 1. Results of the Analysis for Primary and Secondary Outcomes

Analysis	No. of Included Trials	Events/Total Number, Epinephrine Group[a]	Events/ Total Number, Control Group[a]	Risk Ratio/ Mean Difference (95% CI)	*p* for Significance	I^2	*p* for Hetero-geneity
Longest follow-up mortality	12	197/579	219/648	0.95 (0.82–1.10)	0.49	0	0.51
28-/30-d mortality	8	150/468	154/488	1.01 (0.81–1.29)	0.87	26	0.22
Receipt of renal replacement therapy	4	60/264	65/285	1.01 (0.65–1.55)	0.98	34	0.21
Myocardial ischemia	6	17/362	14/427	1.53 (0.78–3.02)	0.21	0	0.91
ICU length of stay, d	3	220	230	−0.22 (−1.92 to 1.47)	0.80	0	0.98
Post-randomization lactate level, mmol/L[b]	7	184	195	0.13 (−0.30 to 0.55)	0.55	71	0.002
Arrhythmias, overall	8	41/380	44/445	1.20 (0.81–1.77)	0.37	0	0.64
Supraventricular arrhythmias	3	21/191	22/199	1.00 (0.57–1.74)	0.99	20	0.26
Ventricular arrhythmias	5	16/266	12/322	1.47 (0.73–2.99)	0.28	0	0.48
Limb ischemia	4	8/277	10/293	0.83 (0.34–2.06)	0.69	7	0.34
Bowel ischemia	4	2/82	0/130	4.18 (0.47–37.27)	0.20	0	0.79
Stroke	4	4/228	3/284	1.61 (0.43–6.05)	0.48	0	0.64
Heart rate, beats/min[b]	8	204	218	4.81 (−2.00 to 11.62)	0.17	82	< 0.001

[a]Only total number is reported for continuous variables.
[b]At 24 hr from randomization, or value closest to 24 hr.

example, in Europe, a vial of epinephrine (0.5–1 mg) costs from less than 0.50 € to 0.85 € and a vial of norepinephrine (2 mg) is about 1.30 €.

On the other side, the epinephrine-induced increase in blood lactate should also be considered. The increase in lactate levels associated with epinephrine use is already documented and may be clinically relevant, given the well-recognized role of lactate as a marker of tissue perfusion in critically ill patients (2, 34–37). However, there is also general agreement that the epinephrine-induced increase in lactate is not associated with reduced tissue perfusion or harm, as also confirmed by our meta-analysis (38, 39). Nevertheless, it seems reasonable to use agents other than epinephrine in order to avoid potential confounders in monitoring lactate levels and hence adequacy of resuscitation. Of note, our analysis, in which we analyzed lactate levels at 24 hours from randomization, confirmed that increase in lactate associated with epinephrine use is generally transient. Interestingly, we found lower lactate level in pediatric patients receiving epinephrine. This finding might be related to the fact that patients in the epinephrine group achieved hemodynamic stabilization earlier than the control group receiving dopamine in both trials. Accordingly, this might have translated in improved organ perfusion and lactate clearance, despite the effect of epinephrine on lactate production.

Our study also confirmed that epinephrine use is associated with a trend toward higher heart rate as compared with control treatments, which might explain the nonsignificant trend toward increased risk of myocardial ischemia. Therefore, our study suggests that epinephrine might be beneficial when increase in heart rate is desirable in order to increase cardiac output but should be used with caution in patients at risk for myocardial oxygen demand/supply mismatch.

We found a possible subgroup interaction effect in serum lactate levels between trials performed in the setting of sepsis and other settings, with higher lactate level in the nonseptic group. However, data from nonseptic trials derived from one small, single trial in patients with cardiogenic shock. Therefore, we believe these results should be interpreted with caution. Furthermore, we observed lower lactate level in septic pediatric patients receiving epinephrine as compared with control group, which contributed to this heterogeneity. Of note, data from the largest trials performed in adults in this setting were not included in the lactate analysis, as data in the original manuscripts (which clearly show higher lactate levels in the epinephrine group) were presented as figure only and no raw numbers were available for pooled analysis.

Our study has some limitations. We included RCTs performed in both adult and pediatric patients and in different clinical settings. However, statistical heterogeneity was low in most of the analyses, and subgroup analyses did not suggest relevant interactions with the exception of the lactate levels discussed above. Control treatment was too heterogeneous to perform adequate subgroup analyses; therefore, we cannot comment on specific comparisons between epinephrine and other vasoactive agents.

The dose of epinephrine was also variable, and not amenable to pooled analysis, although most of the trials investigated doses in the range of 0.1–0.3 μg/kg/min, which is consistent with clinical practice. Finally, meta-analyses should be considered hypothesis-generating rather than confirmative. Notably, while epinephrine is frequently used in everyday clinical practice in ICUs, we were able to identify only 12 RCTs (enrolling a total of 1,227 patients) reporting mortality data. Therefore, adequately powered multicenter RCTs are required before definitive answers on epinephrine efficacy and safety can be provided.

CONCLUSIONS

Continuous infusion of epinephrine as inotrope/vasopressor is not associated with worse clinical outcomes in critically ill patients. A transient increase in serum lactate is commonly observed as compared with other vasoactive drugs in adult patients. A nonsignificant increase in heart rate, myocardial ischemia, and ventricular arrhythmias has also been observed. Intensive care physicians should chose vasoactive agents according to the specific hemodynamic effects desired, their clinical experience with each specific agent, and available resources.

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